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Abstract Title:- Pharmacogenetic association of CYP2C19*2 (rs4244285) polymorphisms in determination of high on-treatment platelet reactivity (HTPR) in Coronary Artery Disease (CAD) patients - An experimental and Meta-Analysis investigation

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Aims:-In South Indian CAD patients, data regarding the relationship between the CYP2C19*2 gene polymorphism and clopidogrel resistance is scarce, and it is uncertain how the HTPR assigned by various PFTs' with variable cut-offs associates with CYP2C19*2 gene polymorphism. Hence the current study evaluated the clopidogrel resistance and their association with CYP2C19*2 gene polymorphism in South Indian CAD patients. A meta-analysis in global population with the association of clopidogrel resistance with CYP2C19*2 gene polymorphism was assessed.

Methods:- SNP genotyping of CYP2C19*2 polymorphism was done using 5'-hydrolysis chemistry by TaqMan® Drug Metabolism Genotyping Assays (DME) (Applied BiosystemsTM, USA). The platelet function test (PFT) using Vasodilator Stimulated Phosphoprotein Phosphorylation- Enzyme Linked Immunosorbent Assay (VASP-ELISA) was done to identify the Clopidogrel resistance/HTPR status in CAD patients (n=196) cohort. Meta-analysis was performed using free web-tool MetaGenyo software for global comparison of the association CYP2C19*2 (rs4244285) and clopidogrel resistance. Statistical analysis was carried out using IBM® SPSS® software, v.22.0 (IBM, USA).

Results:- The carriers of the Loss-of-function (LOF) of CYP2C19*2 (rs4244285) had 1.7-fold greater risk of developing HPTR in additive model. The non-additive genetic relationship between co-dominant (GG vs. GA) and dominant (GA+AA vs. GG) models of CYP2C19*2 (rs4244285) indicated 2.6 and 2.5 times elevated risk that favours HTPR respectively. Meta-analysis demonstrated that the LOF of CYP2C19*2 contributes to clopidogrel resistance favouring HTPR. The association didn't not deviate after the adjustment with ethnic groups, diagnosis standards of clopidogrel non-responders/HTPR and clopidogrel dosage (75mg, 300mg, & 600mg/day)

Conclusions:- This is the first study to evaluated clopidogrel resistance using most reliable ELISA method for platelet function test in South Indian CAD patients. The present shows that CYP2C19*2 polymorphism associated with clopidogrel resistance/HTPR and meta-analysis study suggest that LOF of CYP2C19*2 associated to clopidogrel resistance regardless of diverse ethnicity, diagnosis standards of clopidogrel non-responders, clopidogrel dosage and different the platelet function tests used. Future research must use a common definition of clopidogrel resistance in order to develop personalized guided therapy based phenotypes, however genotype guided antiplatelet therapy may be useful for therapeutic decisions.

Keywords:- Coronary artery disease, single nucleotide polymorphism, clopidogrel response, CytochromeP450